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Development of adaptive immune cells and receptor repertoires from infancy to adulthood

Johannes Trück[1] and Mirjam van der Burg[2]

Abstract

The human adaptive immune system is learning throughout lifetime, which is associated with extensive alterations in the absolute numbers and cellular compositions of the lymphocyte compartment and dynamic changes in adaptive immune receptor repertoires. Early in life, naïve lymphocytes dominate the peripheral blood cell compartment while memory B and T cells remain quite stable in numbers with age. However, these memory cell compartments undergo profound transformations characterized by accumulation of mutations in rearranged immunoglobulin genes and other changes, all leading to a more mature adaptive immune receptor repertoire. Increasing knowledge of the normal adaptations of the adaptive immune system with age now allows a better understanding of the biology of health and providing reference data for the use in biological and clinical practice.

Addresses

[1] University Children's Hospital Zurich, Switzerland

[2] Department of Pediatrics, Laboratory for Pediatric Immunology, Leiden University Medical Center, Leiden, the Netherlands

Corresponding author: van der Burg, Mirjam (m.van_der_burg@lumc.nl)

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Keywords

B cells, T cells, Infants, Age-dependent dynamic, Adaptive immune receptor repertoires, Istoype, Maturation, Somatic hypermutation, Diversity.

Introduction

The human adaptive immune system plays an important role in establishing defense mechanisms against foreign structures such as viral or bacterial pathogens, which would otherwise lead to significant infections. After birth, young infants are protected by passively transferred maternal immunoglobulin type G (IgG) before they have produced significant amounts of their own immunoglobulins at around 3 months of age. The innate immune system is also not yet fully formed at birth but matures rapidly and, compared with the adaptive immune system, offers an early, but less targeted, barrier against invading pathogens without previous exposure [1]. In contrast, the adaptive immune system evolves gradually over time and through repetitive antigen exposure, which eventually leads to antigen-specific memory that protects the host in the long run. Its main players are B and T lymphocytes, and these specialized cells are equipped with antigen-specific B-cell and T-cell receptors and confer humoral and cellular immunity, respectively, through clonal expansion and further cell differentiation. Both types of adaptive immune receptors consist of chains made of several elements and rearranged from germline-encoded genes. This mechanism, called VDJ recombination (V for variable, D for diversity, and J for joining gene), already produces a large number of naïve lymphocytes with diverse receptors, collectively called the adaptive immune receptor repertoire (AIRR). Further diversification of B cells is achieved by introduction of point mutations (somatic hyper mutations) of receptor chains upon antigen exposure leading to improved antigen-receptor binding and hence affinity maturation. Similarly, antigen encounter can change the type of Ig heavy chain constant region (called class switch recombination), affecting the effector function of the B-cell receptor.

Detailed phenotyping of lymphocytes and characterization of their receptor sequences offer important information into adaptive immune processes and how they mature with age. Here, we summarize the development of the adaptive immune system from infancy to adulthood, focusing on age-related changes in lymphocyte compositions and reviewing results from AIRR sequencing studies in humans.

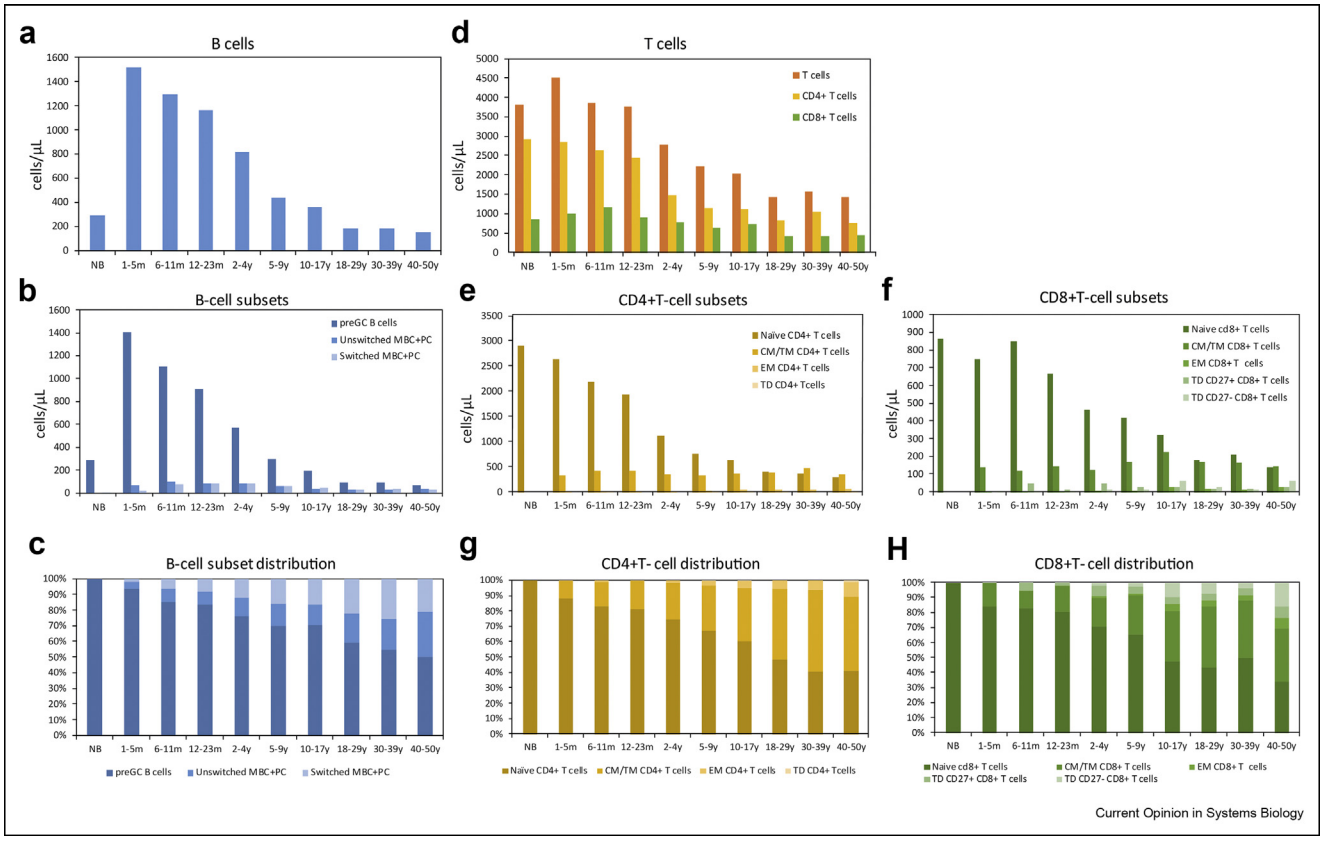
Age-dependent dynamic of the lymphocyte compartment

Previous work has demonstrated a strong age-dependent dynamic that is observed when measuring peripheral blood lymphocyte subsets of healthy humans [2,3]. However, this dynamic is different for B and T lymphocytes. The absolute number of total B cells increases rapidly after birth and gradually decreases to reach a

plateau during adulthood (Figure 1a). A peak in the absolute numbers of total B cells is observed between birth and 5 years of age, mainly due to a high number of naïve (pre-germinal center) B cells (Figure 1b). This high number of B cells in infants and toddlers is most likely related to a developing naive immune repertoire. The proportion of both unswitched and switched memory B cells slowly increases with age, although the total amount of memory B cells remains quite stable (Figure 1c). Even above the age of 18 years, the proportion of memory B cells shows an increase, indicating a continuous maturation and shaping of the adaptive immune system well into adulthood. Within the switched memory B-cell compartment, the proportion of immunoglobulin isotypes also changes with age [2]. The human immunoglobulin heavy-chain (IGH) gene constant region can be divided into three gene blocks containing the constant regions for IgM and IgD (1st block); IgG3, IgG1 and IgA1 (2nd block); and IgG2, IgG4 and IgA2 (3rd block). The peak of switched memory B cells expressing IGH isotypes of the 2nd block can be observed between the age of 2 and 4 years, whereas the maximum value of switched memory B cells expressing isotypes of the 3rd block is seen only during adulthood. These observations are supposed to reflect consecutive cycles of IGH class switch recombination through life. These findings on the age-dependent composition of the B-cell compartment [2] are of importance when IGH sequencing is performed on bulk B cells, especially if primers are used that are not reaching deep enough into the IGH constant region and hence capture immunoglobulin isotype information.

The T cell compartment also displays an age-dependent dynamic. The number of total T cells is highest in the first 6 months of life and continuously decreases during childhood to reach lower but stable amounts during adulthood (Figure 1d). This decrease mainly reflects a drop in the absolute number of CD4+ T cells, as the amount of CD8+ T cells is relatively stable. Naive CD4+ and CD8+ are highest at birth and show a steady and strong decrease in the first few years of life to finally reach low and stable levels during adulthood. In contrast, the absolute number of central memory/transitional memory (CM/TM) CD4+ and CD8+ T cells is quite stable throughout life (Figure 1e and f). With a

Figure 1



Age-dependent dynamics in the composition of the B-cell and T-cell compartment. Age-related changes in absolute numbers of B cells **(a)** and B cell subpopulations **(b)**, and the proportion of B-cell subpopulations within the B-cell compartment **(c)**. Absolute numbers of total T cells, CD4+ and CD8+ T cells **(d)**, and CD4+ and CD8+ T-cell subpopulations **(e, f)**, and the proportion of CD4+ and CD8+ T-cell subset subpopulations within the T-cell compartment **(g,h)**. All values represent medians within age groups based on a published data set [3].

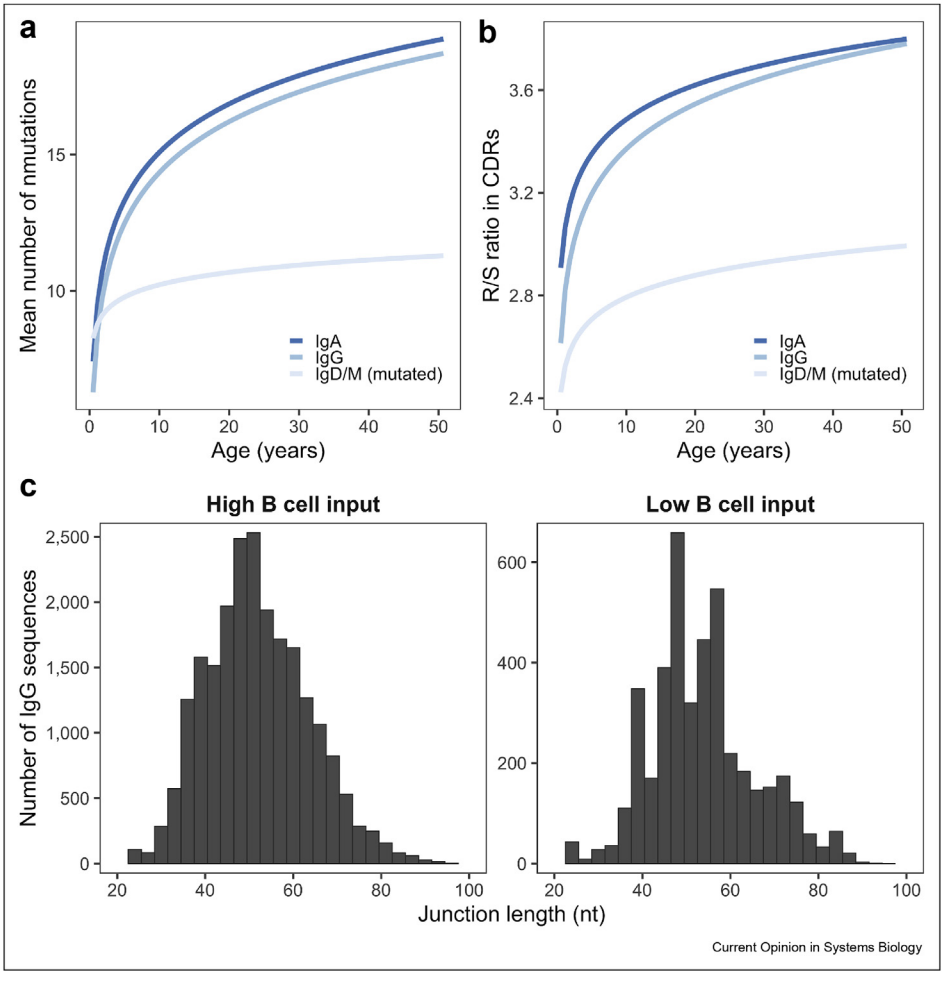
decreasing number of total T cells, the proportion of CM/TM T cells increases (Figure 1g and h). The absolute number of effector memory and terminally differentiated CD4+ and CD8+ T cells are low throughout all age groups, but similarly to CM/TM T cells the proportion of these populations increase later in adulthood (Figure 1g and h).

The values displayed in Figure 1 represent medians observed in a cohort of healthy individuals [3]. However, it should be noted that, especially in childhood, the absolute numbers of these populations may vary from one individual to another, but within an individual there is a similar dynamic. In a large cohort of more than 1000 children between birth and the age of 6 years, the effect of nongenetic parameters including lifestyle-related or immune-mediated determinants, birth characteristics, and infection-related factors on age-related leukocyte dynamics were studied [4]. Breast-feeding and *Helicobacter pylori* colonization appeared to be associated with certain B-cell subpopulations, whereas dynamics of CD4+ T cells were predominantly associated with birth characteristics and both CD4+ and CD8+ T cell dynamics with persistent infections due to cytomegalovirus or Epstein–Barr virus.

Development of the immunoglobulin heavy-chain repertoire

Similarly, studies investigating the immunoglobulin repertoire found significant changes in childhood, characterized by alterations in gene usage, mutations, and other global repertoire features [5,6]. There is limited data on the extent and the dynamic of age-associated changes in the T-cell receptor repertoire;

Figure 2



Human immunoglobulin heavy-chain (IgH) sequencing data are affected by age of study population and cell numbers of input samples. Age-related changes in **(b)** somatic hypermutation and **(b)** the replacement-to-silence (R/S) ratio in complementary-determining regions; data from the study by Ghraichy et al. [6]. **(c)** Distribution of IGH junction lengths of IgG repertoires in human peripheral blood samples containing a higher (1.04 Mio) compared with a lower (0.12 Mio) number of B cells (J. Trück, unpublished).

therefore this review focuses on the age-related effects on B-cell immunoglobulin heavy-chain sequencing data. Similar to findings in cell populations, there is an increase in the proportion of mature, antigen-experienced B-cell responses in older people compared with younger individuals [6]. It has been shown that somatic hypermutation and class-switch recombination occur throughout gestation and although B-cell repertoires of newborns are very diverse they are still dominated by naive, unmutated IGH sequences [7]. IGH sequences from children accumulate somatic hypermutations most extensively in the first 10 years of life in IgA/IgG switched memory compartments (Figure 2a). The mean number of mutations of IgD/M repertoires follows a similar age trend to IgA/G repertoires although levels are reached earlier and remain low throughout adulthood (Figure 2a). In addition to an accumulation of mutations, there is a strong positive selection of IGH sequences in older individuals, which seems to even exceed the speed at which somatic hypermutation occurs with age (Figure 2b). Similar to somatic hypermutation, positive selection of IgD/M repertoires remains lower than switched repertoires across all ages (Figure 2b). B-cell receptor repertoire sequencing data are increasingly used for structural prediction models [8,9]. These data can help to interpret the function and specificity of antibody sequences and therefore allow additional insight into B-cell responses. Antibody structures can be predicted from high-throughput repertoire data and compared with predicted germline structures. When previously assessed in a group of healthy individuals, the proportion of sequences that structurally diverge from germline greatly increased with age in all switched isotype subclasses, further supporting the functional impact of accumulated mutations throughout childhood [6].

Normative data of IGH repertoires are not only helpful in understanding biology and serve as reference data, for example, when sequencing is performed on patient material, but can also provide highly relevant information during interpretation of IGH repertoire data. For example, although repertoire diversity can be easily measured using all kinds of low- and high-throughput sequencing data, it remains challenging to compare the diversity between biological samples as it is heavily influenced by sequencing and analysis methods, and, more importantly, by the number cells in a given sample. High numbers of B cells will automatically give a higher diversity than when a lower number of B cells are put into the assay (Figure 2c). However, cell numbers are often not known so that this measure has to be interpreted with caution, especially in clinical samples.

Conclusions

Both the cellular composition of the lymphocyte compartment and the antigen-dependent characteristics of AIRR undergo extensive changes from birth to adulthood. These age-related dynamics and the maturation of the lymphocyte as a whole have been studied in detailed in recent years. Findings from these studies now allow a better understanding of the biological processes associated with accumulating antigen exposure over a lifetime and also provide reference data that can be used to evaluate patient samples, opening up new opportunities in both biological and clinical practice.

Conflict of interest statement

Nothing declared.

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